parameter	baseline	1mcg/kg - dexmedetomidine		prazosin	atipamezole
		peak	15 min		
SVR goat	2950	4823	3253	2168	1602*
SVO2 (HF)	0.69	0.60#	0.68	0.67&	0.71
SVO2(CU)	0.67	0.45*+	0.55*	0.58*	0.67+
SVO2 goat	0.70	0.57	0.61	0.42*	0.78
AVO2(HF)	0.25	0.37*	0.29	0.29&	0.26
AVO2(CU)	0.29	0.52*	0.42*	0.48*	0.38*
AVO2 goat	0.28	0.41	0.35	0.52*	0.19

* $p<0.05$ vs baseline; # $p<0.05$ dogs HF compared to dogs CU;
& $p<0.05$ dog HF vs goat; + $p<0.05$ dogs CU vs goat

Summary:
The cardiovascular effects of dexmedetomidine start with peripheral vasoconstriction by alpha$_2$ stimulation. Upon entering the CNS, dexmedetomidine alpha$_2$ stimulation initiates a centrally mediated sympatholytic effect and hypotension predominates due to the reduced heart rate and contractility.

Dexmedetomidine had similar effects on heart rate and cardiac function in different model systems with differing species and anesthetics. However, the changes in blood pressure and vascular resistance did differ, indicating anesthetic can influence the sympatholytic action. The CU dogs had high sympathetic activity and the hypertensive response was shorter than in the HF dogs although the systemic vascular resistance did not differ.

There were also species differences which may be due to different numbers of vascular alpha$_2$ receptors. In the goat, smaller increases in vascular resistance and shorter duration of hypertensive responses were seen than observed in the dog. This was also accompanied by a smaller decrease in arterio-coronary oxygen saturation.

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[17]

Study Title: Comparison of the hemodynamic and coronary vascular effects of dexmedetomidine and clonidine in the anesthetized dog. In: The effect of dexmedetomidine on the circulation and the normoxic and ischemic heart

(#61)

Vol #26, and page #001:

NDA 21-038

Conducting laboratory and location [redacted]

Date of study report: 1991, 1992

Methods:
Healthy mongrel dogs, 15, were used in the study. They were premedicated with fentanyl, anesthesia induced with thiopental and maintained with 40%/60% oxygen:nitrous oxide and halothane when necessary to maintain the depth of anesthesia. The dogs were intubated, mechanically ventilated and additional fentanyl was supplied to maintain heart rate between 80 and 100 BPM. After instrumentation and stabilization, 8 dogs received clonidine in increasing doses of 1, 3, 10 and 30 mcg/kg and 7 dogs received dexmedetomidine at 0.1, 0.3, 1, 3 and 10 mcg/kg. The recording of effects was at the peak, 1-2 minutes, and at 15 minutes postdosing. After recovery from either treatment, the dogs were injected with the alpha$_1$-antagonist prazosin, 100 mcg/kg, and the ascending doses of clonidine or dexmedetomidine and the measurements were repeated. Finally, the dogs were injected with the specific apha$_2$-antagonist atipamezole, 250 mcg/kg and the measurements repeated. The measured parameters were mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), systemic vascular resistance (SVR), mixed venous oxygen saturation (SVO2), coronary flow (CF), coronary vascular resistance (CVR), coronary venous oxygen saturation (CVO2) and first positive derivative of left ventricular pressure (LVdp/dtmax).

Results:
MAP: The pressure initially increased with both clonidine and dexmedetomidine in dose-dependent manner and all MAP had returned to normal by 15 minutes, except for dexmedetomidine at 10 mcg/kg. Dexmedetomidine was about 3x as potent as clonidine.
HR: There were dose related decreases in HR with both compounds. At the highest dose of each compound, superventricular and ventricular extrasystoles were seen immediately after injection.
CO: The cardiac output declined in dose related fashion with both compounds. The highest dose of clonidine induced a 60% decrease and with the highest of dexmedetomidine the CO was reduced 57%.
SVR: The resistance increase was dose related with both compounds and the highest dose of clonidine increased the resistance by 260% and dexmedetomidine, by 230%.
SVO2: These changes paralleled the changes in cardiac output, but less pronounced.
CF: the coronary flow was little changed, only reduced 15 min after clonidine at 30ug/kg.
Effects of prazosin, alpha$_1$-antagonist: CO and SVR were reduced while coronary flow, coronary vascular resistance and CVO2 returned to baseline. Lvdp/dtmax was further reduced in clonidine dogs but recovered in dexmedetomidine dogs.

Effects on Atipamezole - alpha$_2$-antagonist: a greater decrease in MAP was observed in the dexmedetomidine dogs but the HR increase was greater in the clonidine dogs. CO returned to baseline in clonidine dogs but remained low in the dexmedetomidine dogs.

NDA 21-038

Summary:
The hemodynamic effects of dexmedetomidine are similar to clonidine effects in anesthetized dogs. The investigators state "good clinical results achieved with alpha$_2$ agonists may be due to their use in doses which cause sympatholysis without too much vasoconstriction."

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[18]

Study Title: Changes in cardiac function induced by dexmedetomidine, as determined by pressure-volume analysis. In; The effect of dexmedetomidine on the circulation and the normoxic and ischemic heart

(#65)

Study No: not stated
Vol #26, page #054:
Conducting laboratory and location: [redacted]

Date of study report: 1991, 1992 [redacted]

Methods: The experimental protocol was copied from the submission (V26/pg 055-059): Nine dogs were used in this protocol, which were premedicated with 200 mcg/kg fentanyl im. Anesthesia was induced by 30 mg/kg thiopental iv. The animals were ventilated with oxygen in nitrous oxide (40/60) with 0.5-1.0 % Halothane.

Pressure-volume analysis
Two left ventricular catheters were introduced via the left atrium, one to measure pressure by tip-micro manometer, the other to measure volume by conductance. The position of the tip of the conductance catheter in the apex was verified by inspection of the segmental conductance signals; a correct position was assumed if the signals from at least the four most distal segments displayed a typical phasic left ventricular volume tracing. If the most proximal segment reflected typical phasic atrial volume changes, this segment was excluded from the calculation of total ventricular volume. Correct positioning of the conductance catheter was further facilitated by on-line display of the left ventricular contour, derived from the five segmental conductance signals.

Left ventricular volume measurement
The conductance catheter determines left ventricular volume (V_{lv}) on-line by measuring time-varying electrical conductances of five segments of intraventricular blood. Total ventricular volume is calculated from these measurements using formulas which have been described previously. The pigtail catheter used was especially designed and equipped with ten electrodes. The electrodes, each 1 mm long were spaced to have the distance between electrodes 1 and 8

match the left ventricular base to apex dimension. In practice they were 10 or 11 mm apart depending of the size of the heart and the catheter used. An alternating current of 0.03 mA at 20 kHz passed through electrodes 1 (apex) and 8 (mitral valve) and voltages were measured between the five adjacent electrode pairs 2-3 through 6-7, from which five conductances were calculated. Electrodes 9 and 10 were not used. An analog signal conditioner-processor (Sigma5. Leycom. Oestgeest. The Netherlands) provided the current source and processed the segmental conductances producing an on-line display of the left ventricular contour as well as a continuous and instantaneous volume signal. The volume signal was combined with the LV-pressure signal on a X-Y oscilloscope in order to display instantaneous pressure-volume loops continuously. To obtain correction on the volume signal for parallel conductance caused by tissues surrounding the left ventricular cavity, a bolus of 5 ml hypertonic saline (10%) was injected in the central venous compartment. As the bolus mixes with the fluid in the ventricular cavity, its conductivity increases, causing the overall conductance signal to increase while the parallel component remains constant. End-systolic overall conductance then is plotted as a function of end-diastolic overall conductance during the mixing of the bolus and the parallel conductance is equal to the intersection point between the regression line of these values and the line of identity. This procedure was performed before and after administration of dexmedetomidine during 10 sec. of respiratory arrest to avoid ventilation induced changes in LV pressure and volume. Blood resistivity was measured by 5 ml blood in a four electrode cuvette prior to a preload reduction in the assessment of ESPVR, in order to correct for changes caused by temperature and hematocrit. The conductance stroke volume was calibrated over three respiratory cycles at each sample time by stroke volume simultaneously measured by the thermodilution technique. Possible inaccuracies in determining the parallel conductance were avoided since comparisons were made in the same animal, before and after cardiopulmonary bypass.

Experimental protocol

Each pressure-volume analysis consisted of triple measurements of cardiac output left ventricular conductance and pressure during periods of ventilatory arrest and measurement of left ventricular conductance and pressure during a 10 sec occlusion of the inferior caval vein, during and after ventilatory arrest.

After baseline measurements had been performed in this way, the left anterior descending coronary artery (LAD) was completely occluded during 2 minutes using a tantalum clamp (n=3) or narrowed for 15 min using an inflatable occluder. The pressure-volume analysis was repeated after 1 min occlusion or 12 min coronary stenosis (sample 2) and 15 min after release of the occlusion or stenosis (sample 3). After these measurements, dexmedetomidine was administered iv at a dose of 1 mcg/kg over 2 min. Fifteen min later pressure-volume analysis was repeated during normal perfusion (sample 4), during another period of ischemia (either occlusion or stenosis. sample 5), and 5 min after release of the coronary obstruction (sample 6).

Results:
The data on cardiac output and end-systolic (Ees) and end-diastolic elastance (Ed) are presented in Table 065- 1. Dexmedetomidine significantly decreases cardiac output (by approximately 40%). whereas regional ischemia (induced by either coronary occlusion or stenosis) did not affect this variable.

Regional myocardial ischemia did not affect Ees and Ed. In contrast. dexmedetomidine (1 mcg/kg) tended to decrease Ees and significantly increased Ed. Fifteen min after dexmedetomidine 1mcg/kg (sample 4), Ees was on the average 30% lower than at baseline (sample 1) and 15 min after the first period of ischemia (sample 3; $p<0.08$ in both cases). Subsequently, Ees showed a tendency to increase during ischemia (sample 5) as well as after subsequent reperfusion (sample 8). Ed increased by approximately 70 % after administration of dexmedetomidine ($p<0.05$ at samples 4 and 5, compared to samples 1 and 2). The data in the following table was extracted from the submission (V26/p62):

Table 065-1:

	End-Systolic Elastance (mmHg/ml)	End-Diastolic Elastance (mmHg/100ml)	Cardiac Output (l/min)
baseline	1.41 (0.61)	10.8 (3.0)	4.77 (1.08)
ischemia	1.24 (0.40)	9.8 (2.2)	3.80 (0.70)
recovery - 15 min	1.49 (0.59)	10.5 (2.0)	3.83 (0.74)
dexmedetomidine 1 mcg/kg	0.92 (0.34)	16.7 (6.4)*	2.87 (0.59)*
ischemia	1.25 (0.24)	18.0 (5.7)*	2.63 (0.38)*
recovery - 15 min	1.47 (0.09)	12.4 (4.0)	1.90 (0.57)*

* $p<0.05$ compared to corresponding sample time before administration of dexmedetomidine

Summary

The results indicate that dexmedetomidine reduces contractility and the ability of the left ventricle to fill. The effects are most likely related to the sympatholytic activity and are energy sparing of the heart. However, this should be considered when used in patients with impaired cardiac function.

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NDA 21-038

[19]

Study Title: Comparison of hemodynamic stabilizing effects of dexmedetomidine and esmolol (#70)

Vol #26, and page #080:
Conducting laboratory and location: [redacted]
Date of study report: July 1997

Methods: The methods were extracted from the submission (V26/p83-86):
Animal preparation and instrumentation
All experiments were performed in accordance with the "Guiding Principles in the care and use of animals" as approved by the counsel of the American Physiological Society and under the regulations of the Animal Care Committee of the University of Limburg. Eleven adult mongrel dogs either sex weighing 20 - 40 kg were anesthetized with an intravenous injection of thiopental (25 mg/kg) and intubated with a cuffed tube. They were connected to a volume controlled respirator and ventilated at a rate of 16 breaths per minute (5 cm H_20 PEEP). During preparation and instrumentation, anesthesia was maintained with 1% halothane in oxygen/nitrous oxide (33% 0_2/67% N_20). End-expired carbon dioxide concentration was continuously monitored by a capnograph ([redacted] . Arterial blood gases were frequently analyzed during the study (ABL 3 radiometer), and when necessary, ventilation was adjusted or sodium bicarbonate solution (4.2%) was administered intravenously. Body temperature was kept between 37 and 39 °C by means of a thermostatically regulated heating pad. Fluid (NaCl, 0.9% or Haemaccel), was administered intravenously in order to keep end-diastolic left ventricular pressure between 5-10 mmHg. Heart rhythm was monitored from lead II of the electrocardiogram.

Balloon catheters for variation of pre- and after-load were introduced through a jugular vein into the inferior caval vein and through a femoral artery into the thoracic aorta, respectively.

Left ventricular cavity and ascending aortic pressure were measured with a double sensor catheter-tipped micro manometer inserted via the right femoral artery. To enable pressure calibration during the experiment, the fluid-filled lumen of the catheter-tipped micro manometer was connected via a three-way cock at the level of the left atrium to an external pressure transducer.

Left and right common carotid arteries were dissected free over a distance of about 1.5 cm and care was taken to ensure that nerve branches from the vagosympathetic trunk remained intact. Umbilical tape was placed loosely around each carotid artery, and the two ends of the ties were passed through stiff plastic tubing to form a snare occluder. Left carotid pressure was measured with a catheter introduced into the cranial thyroid artery connected to a pressure transducer.

The chest was opened through the left fifth intercostal space and the heart was suspended in a pericardial cradle. An ultrasonic transit-time flowprobe ([redacted]) was placed

around the proximal part of the left descending coronary artery (LDCA) for measurement of phasic and mean coronary blood flow. To obtain coronary venous blood a polyethylene catheter was inserted into a coronary vein of the perfusion area of the LDCA. For measurement of regional myocardial mechanical function, three inductive coils were sutured to the epicardium of the left lateral ventricular wall in an equilateral triangle configuration. The area decrease of the epicardial region enclosed by the coils was calculated from the relative length changes in the three different directions. Assuming that the volume of a myocardial wall segment does not change during the cardiac cycle, systolic area decrease is directly related to systolic wall thickening.
For continuous beat to beat measurement of aortic flow, a transit-time flowprobe was placed around the ascending aorta. A pulmonary artery catheter was introduced via the left jugular vein into the pulmonary artery and connected to a thermodilution cardiac output computer (——————). During the experiment cardiac output, as obtained by averaging triplicate thermodilution values was compared regularly with the aortic flow measurement. These were always in accordance with each other.

Hemodynamic data analysis
All hemodynamic signals were preamplified and then digitized with a 16 channel, 12 bit interface in an IBM-AT Compatible PC. The sampling frequency was 200 Hz for each channel. These signals were continuously displayed on the computer screen, and stored on the hard disk for off-line processing. The calculated hemodynamic variables were displayed real time on the computer screen as well and at sample times were stored on the hard disk. The amplifiers and software were developed in the ——————→ of the University of Maastricht. The stored data were further processed as a datafile for Microsoft EXCEL.

Peak of first derivative of left ventricular pressure (LVdP/dtmax) and end diastolic left ventricular pressure (LVEDP) were calculated from the left ventricular pressure signal. Systemic vascular resistance (SVR) was calculated as the ratio of mean aortic pressure and aortic blood flow. For the measurements during the protocol, the average of each hemodynamic variable over a stable hemodynamic period of 30-60 seconds was calculated.

Analysis of laboratory parameters
Arterial (A) and coronary venous (CV) blood gas tensions were assessed with a radiometer blood gas analyzer. Hemoglobin content (Hb) and oxygen saturation (O_2sat) were assessed with a radiometer OSM-2 hemooxymeter, Blood oxygen content (O_2cont.(mmol/l), myocardial oxygen extraction (MO_2 extr.) and myocardial oxygen consumption (MVO_2, mmol /ml.min.100g^{1}) were calculated as:

O_2cont (Hb(mmol/L) (O_2sat) + (0.0102 (P 0_2 (kPa)).
MO_2extr = ((O_2cont (A) - O_2cont (CV))/O_2cont (A)
MVO_2 ((O_2cont (A) O_2cont (CV)in mmol/L) (coronary flow (L/100g)

For determination of plasma catecholamine and dexmedetomidine levels, arterial blood samples were collected in chilled propylene tubes. The tubes were kept in ice and centrifuged within 30 minutes at + 4 °C to separate the plasma. The plasma samples were stored at -70 °C until analyzed. Plasma concentrations of endogenous catecholamines noradrenaline (NA) and adrenaline (A) were assayed using high performance liquid chromatography with coulometric electrochemical detection. Intra-assay coefficients of variation with this method are 2% for NA and 10% for A. Plasma concentrations of dexmedetomidine were analyzed at the pharmacokinetics laboratory Orion Corporation.

Experimental Protocol

After surgical preparation halothane anesthesia was changed into α-chloralose anesthesia (intravenous loading dose 40 mg/kg maintenance 8 mg/kg/h). Chloralose was dissolved in water to a concentration of 7.5 mg/ml. Thereafter, the animals were ventilated with 30% oxygen in room air and all dogs were allowed to stabilize for at least 60 minutes.

All experimental medication was given through the proximal infusion port of the pulmonary artery catheter. At first esmolol HCl was administered as bolus dose of 500 µg/kg/min for 2 minutes followed by a continuous infusion of 300 ug/kg/min. Every dog was examined if the above mentioned regimen resulted in a complete B_1-adrenergic blockade. This was done as follows. Before administration of esmolol we assessed that 13±2 ug/min of isoprenaline was needed to increase heart rate more than 20%. During esmolol (300 ug/kg/min) this dose of isoprenaline caused a heart rate increase of less than 5%.

Subsequently dexmedetomidine (dissolved in NaCl 0.9%) was administered with a target plasma concentration of 0.5 ng/ml. To this purpose a bolus of 1 ug/kg was given over 20 minutes, followed by a continuous infusion of 1.5 ug/kg/hour during 30 min, 0.4 ug/kg hour during the next 30 min, 0.2 ug/kg/hour during the next 60 min and 0.1 ug/kg/hour during the remainder of the experiment. The doses of esmolol and dexmedetomidine used were shown to attenuate hemodynamic stress reaction for esmolol and for dexmedetomidine.

During esmolol and dexmedetomidine infusion three kinds of measurements were performed:

1)-steady state measurements of all hemodynamic variables and blood sampling for arterial and coronary venous oxygen content and arterial catecholamine and dexmedetomidine plasma concentrations.

2)-measurements during the last minute of a 3 min bicarotid artery occlusion;

3)-barosensitivity tests: i.e. decrease or increase of aortic pressure by inflation of a balloon in the inferior caval vein or descending thoracic aorta, respectively, with steps of 2 mm. This represents stimulation of all barosensors. The effect on heart rate was recorded.

After the last measurements, during continued dexmedetomidine infusion, also infusion of esmolol was started. After steady state and bicarotid occlusion measurements, esmolol infusion was stopped. Half an hour later the vagolytic agent glycopyrrolate was administered (dose 40 ug/kg iv) , followed by steady state and bicarotid occlusion measurements.

After finalizing the protocol the LDCA was occluded and methylene blue dye was injected intracoronary distal to the occlusion, to mark the perfusion area of the LDCA. Subsequently the animal was killed with an overdose of pentobarbital sodium. The weight of the methylene blue stained portion of the myocardium was determined in order to express LDCA blood flow in ml/min/100g

Statistical analysis:
Values are expressed as the mean and standard deviation. Because of missing values the number of observations was not the same for each variable (n ranging from 8-11). The effect of administration of medication and the effect of bicarotid occlusion at each experimental condition were compared within each animal. The hemodynamic effects of bicarotid occlusion during administration of medication were also compared with those obtained in the period before administration of medication

The non-parametric Wilcoxon Signed Ranked test was used for evaluating statistical significance. In case of multiple comparisons a Bonferroni correction was applied. A value of $p<0.05$ was considered significant.

Results:
Dexmedetomidine decreased HR and increased systemic vascular resistance more than esmolol and these effects were reversed by glycopyrrolate. The circulating catecholamines were decreased by dexmedetomidine and increased by esmolol.

Hemodynamic parameter	units	pre - post esmolol	pre-post dexmedetomidine
AOPsyst - systolic aortic pressure	mmHg	-11 ± 8**	19 ± 14*
HR - heart rate	beat/min	-14 ± 16**	-52 ± 11**
CO - cardiac output	l/min	-0.3 ± 0.4*	-0.4 ± 0.8
dPlv/dtmax	mmHg/sec	-545 ± 219**	-115 ± 310
systemic vascular resistance	mmHg.min/l	2 ± 7	24 ± 21*
Coronary blood flow	ml/min	1 ± 4	-4 ± 5*
coronary oxygen consumption	mmol/min/100 g	-0.02 ± 0.22	-0.01 ± 0.07
plasma noradrenaline	nmol/l	0.25 ± 0.22*	-0.23 ± 0.42*

* $p<0.05$ The analysis is for pre versus post within each column
** $p<0.01$

Hemodynamic parameter	units	BCO changes	BCO + esmolol changes	BCO + dexmedetomidine changes
systolic aortic pressure	mmHg	35 ± 22**	24 ± 11**	13 ± 9**
HR - heart rate	beat/min	10 ± 6**	3 ± 3*	17 ± 14 **
CO - cardiac output	l/min	-0.1 ± 0.6	-0.1 ± 0.25	-0.05 ± 0.16
LvdP/dtmax	mmHg/sec	519 ± 358**	170 ± 117**	121 ± 80**
systemic vascular resistance	mmHg.min/l	8 ± 10*	10 ± 6**	2.4 ± 2.2 *
Coronary blood flow	ml/min	8 ± 6**	4 ± 2**	3 ± 4*
coronary oxygen consumption	mmol/min/100g	0.14 ±0.13*	.08 ± 0.06**	0.08 ± 0.07*
plasma noradrenaline	nmol/l	0.25±0.21**	.26 ± 0.32*	-0.08 ± 0.24

* $p<0.05$ ** $p<0.01$ The analysis is for pre versus post within each column

Bilateral carotid occlusion (BCO) induces a rise in HR, systolic BP, LVEDP, LVdP/dtmax, systolic vascular resistance (SVR), coronary flow, myocardial oxygen consumption and plasma noradrenaline levels. Dexmedetomidine blocked the BCO induced increase in SVR and plasma noradrenaline rise and reduced the increase in systemic SBP and LVdP/dtmax. The BCO induced rise in oxygen consumption and HR were reduced insignificantly by dexmedetomidine. The effects of esmolol were a complete block of BCO induced HR and LvdP/dtmax increase. The esmolol infusion did not block the BCO induced increase in aortic pressure, EDLVP, SVR or plasma noradrenaline.

Summary:

The data indicates the sympatholytic activity of dexmedetomidine contributes to the hemodynamic effects. The reduction in HR was more prominent with dexmedetomidine than with esmolol. While dexmedetomidine increases basal systolic aortic pressure, systemic vascular resistance and basal plasma noradrenaline, esmolol did the opposite. Esmolol and dexmedetomidine reduce the stress induced (BCO) increase in cardiac oxygen consumption, while dexmedetomidine reduces HR independent of the original BP.

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NDA 21-038

[20]

Study Title: Effect of medetomidine either as the racemate mixture or as the individual stereoisomers on the heart rate of anesthetized rats

(#59)

Vol #25, and page #204:
Conducting laboratory and location: [redacted]
Date of study report: July 1989
Methods: The subjects were male Wistar rats, 300 to 500 g. The rats were anesthetized, intubated and ventilated, and the left jugular was cannulated for drug administration and the right carotid was cannulated for blood pressure measurement. Medetomidine , the racemate, and the stereoisomers were studied for hemodynamic effects alone and with receptor blocking agents previously administered. The blocking agents used were: atipamezole ($alpha_2$-antagonist), atropine (mucarinic blocker), propanolol (β-blocker) and hexamethonium (ganglionic blocker). Drugs were administered to the initial 4 rats by slow infusion to determine MED values. Subsequently all administrations were by bolus injection and when blocking drugs were used, the animals were allowed to stabilize for 5 to 10 minutes prior to other drug administrations. The initial dose was the MED (0.3 ug/kg) and the subsequent doses, injected with 15 minutes between administrations, were: 0.3, 1, 3, 10, 30, and 100 ug/kg.

Results:
The MED for reducing heart rate to 300 bpm was 1.7 ± 0.1 ug/kg for the racemate and 0.9 ± 0.02 for dexmedetomidine. The l-isomer was inactive on HR and BP at any dose tested. The MED for raising blood pressure by 50 mmHg was 6.6 ± 1.7 ug/kg for the racemate and 3.9 ±1 for dexmedetomidine.

Atipamezole was very effective in blocking the medetomidine induced HR decrease. At the highest doses tested, 30 and 100 ug/kg, there was only a slight fall in HR. Atropine did not inhibit medetomidine induced bradycardia until the dose was at 3 ug/kg. Propranolol caused a significant drop in HR but did not prevent medetomidine from decreasing it further.

The ganglionic blocker, hexamethonium, with atropine and propanolol completely blocked the bradycardia effect of medetomidine. Atropine appeared to block the high dose medetomidine induced bradycardia and propanolol, the low dose effects. Ganglionic blockade did not prevent the medetomidine induced bradycardia, an indication of peripheral action. This heart rate lowering effect of low doses was blocked by propanolol, indicating $alpha_2$ stimulation to inhibit norepinephrine release.

The medetomidine induced increases in BP were due to $alpha_2$ stimulation as atipamezole blocked this effect. Atropine and atropine + propanolol potentiated the hypertensive effects. After ganglionic blockade, these cholinergic and β-adrenergic blockers had no effect on the hypertensive effects of medetomidine because the blood pressure was low.

NDA 21-038

Summary:

Medetomidine produced a dose-related bradycardia and blood pressure increase. These effects were due entirely to the d-isomer and the l-isomer was completely inactive. The bradycardia induction by medetomidine at high doses appeared to be peripherally mediated as it was not blocked by a ganglionic blocker. However, the authors summary suggests the opposite. The low doses of medetomidine have a hypotensive effect due to bradycardia, but at higher doses the alpha$_2$ stimulation induces vasoconstriction and hypertension.

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[21]

Study Title: Effects of alpha 2-adrenoceptor agonist dexmedetomidine on human platelet aggregation in vitro (#177)

Vol #30, and page #160:
Conducting laboratory and location: [redacted]
Date of study initiation: March 1989

Methods: Blood was collected from healthy adult donors. The blood samples were quickly centrifuged and the platelet rich plasma (PRP) was collected.

Dosing: The PRP was stabilized and the test compounds were dissolved in normal saline. ADP was added at optimal levels and sub-optimal levels, and light transmission through the PRP was the measure of platelet aggregation.

Results: Dexmedetomidine did not cause full aggregation when given alone in 3/5 PRP samples when given alone but suboptimal ADP concentrations with dexmedetomidine (3 umol/l) did induce full platelet aggregation. The EC_{50} was 0.05 umol/l with ADP.

Summary:

The investigators stated that dexmedetomidine is only a partial agonist at platelet alpha receptors became it did not induce full aggregation in 3/5 PRP samples. The addition of ADP with dexmedetomidine did cause complete aggregation in all samples.

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NDA 21-038

[22]

Study Title: The Effects of Dexmedetomidine on Uterine Contraction in Rat

{#4}

Study No: #4 of this submission
Study Source: NDA 21-038 7/06/99 BZ - requested submission (Vol 1/pg 1-67)
Conducting laboratory and location: [redacted]

Methods: *in vitro* testing of rat uteri contractions, in a tissue bath, induced by ascending doses of oxytocin. The uteri were of five different stages of estrus; diestrous, early pro-estrus, late pro-estrus, estrus and met-estrus. In addition estradiol induced estrus uteri were tested and uteri at the 16th day of gestation. Oxytocin dose-responses were generated for each tissue and the minimum concentration to produce the maximum contraction was used with dexmedetomidine concentrations in a cumulative dose response from $1x10^{-7}$M to $3x10^{-4}$M.
Drug, lot#, % purity: dexmedetomidine HCl, Batch OT4321

Results: dexmedetomidine had negligible effects, at any tested dose, on any tissue tested.

Summary

Dexmedetomidine had no significant effect on oxytocin induced contractions of the rat uterus at any stage of the estrus cycle or in uteri from pregnant rats.

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[23]

Study Title: Effect of medetomidine and dexmedetomidine on adrenocortical function in dogs

Study No: 12 in this submission
Study Source: NDA 21-038 7/06/99 BZ - requested submission (vol 1/pg. 1-240)
Conducting laboratory and location: [redacted]
Date of study initiation: May 1988

Methods: Groups of beagle dogs, male and female were treated either acutely or chronically with saline, medetomidine, dexmedetomidine or etomidate. the acute administrations were by im injection, 30 minutes prior to ACTH injections. The chronic treatments were with implanted subcutaneous osmotic pumps for 7 days. The change in ACTH induced cortisol was measured.

Results: The groups and results are presented in the following tables from submission (V1/pgs 241A, 241B)

Acute Treatments (N)	Plasma cortisol (nmol/l)	
	time 0	60 min post ACTH
Saline (11)	11.4 ± 2.6	94.4 ± 5.7
medetomidine, 80 ug/kg (3)	17.4 ± 1.0	80.2 ±10.3
dexmedetomidine 80 ug/kg (6)	6.1 ± 2.3	76.0 ± 8.7
etomidate 1 mg/kg (4)	7.5 ± 1.7	13.3 ± 2.9*

Chronic (7days) Treatment (N)	Plasma cortisol (nmol/l)		
	before infusion	before ACTH	60 min post ACTH
Saline (5)	14.5 ± 4.9	9.1 ± 4.1	115.4 ± 2.8
dexmedetomidine			
3 ug/kg/h (4)	8.8 ± 3.5	11.1 ± 3.7	84.6 ± 6.4*
10 ug/kg/h (4)	11.7 ± 4.0	12.7 ± 1.9	69.6 ± 10 *

* $p<0.01$

Summary

The suppression of the adrenal response to ACTH was not significant with dexmedetomidine on an acute basis, but a significant 27% to 40% reduction in ACTH stimulated cortisol was observed after one week of treatment.

##########

APPEARS THIS WAY
ON ORIGINAL

Summary of Pharmacology, Efficacy Studies

The binding studies demonstrated that dexmedetomidine is very potent as an α_2-agonist, and does not significantly interact with ion channels, cholinergic, dopaminergic or GABA receptors and does not inhibit monoamine oxidase.

Sedation - Primary Efficacy Measure
Dexmedetomidine is sedative in mice (30µg/kg iv) and rats (10 µg/kg iv). It increased the hexobarbital (10 µg/kg), thiobarbital (6µg/kg sc) and ethanol induced sleeping times in mice. It increased the effectivness of volatile anesthetics, decreasing the MAC for halothane (10 µg/kg i.v., rats and dogs) and isoflurane (30 µg/kg in mice iv). The sedation is accompanied by motor incoordination as measured by the rotorod test in mice (3 µg/kg, i.v.).

Analgesia
The analgesic effects have been demonstrated in mouse writhing (6 µg/kg iv) and hot-plate tests (3 µg/kg iv), and rat tail-flick tests (3 µg/kg iv).

Anxiolytic
The anxiolytic effects of dexmedetomidine were observed in the Geller Conflict test with rats (0.3µg/kg s.c.). In mice it increased exploration (1.0 µg/kg s.c.) and rearing as an anxiolytic (2 µg/kg s.c.).

Summary of Safety Pharmacology

CNS protective effects
Dexmedetomidine was shown to reduce ischemic brain damage in rats (3 µg/kg i.v.). However there was no anticonvulsant effect against electroshock or pentelenetrazole induced convulsions at doses to 600 µg/kg i.p. in mice and it was also inactive against amygdaloid-kindled seizures in rats at 4 µg/kg s.c..

Hypothalamic-Pituitary-Adrenal Axis
Dexmedetomidine did not alter ACTH stimulated cortisol release in dogs on an acute basis at 80 µg/kg s.c.. However, after a week of treatment at 3 µg/kg/hr s.c. infusion, the ACTH induced cortisol release was reduced by 40%.

Cardiovascular effects
The α_2-agonist effects cause an initial, transient, rise in blood pressure due to vasoconstriction (6 µg/kg in rats, 0.3 µg/kg in monkeys and 1.0 µg/kg in dogs) and this was followed by a fall in blood pressure and the heart rate is reduced. These effects are seen with dexmedetomidine, but

not levomedetomidine. The decreased heart rate, at 1 μg/kg iv in dogs, was accompanied by decreased myocardial contractility, reduced cardiac output and reduced oxygen demand by the heart, as indicated by increased AV O_2 saturation.

Liver - pancreatic effects
Dexmedetomidine transiently increased blood glucose in rats (10 μg/kg i.v.) and gerbils at 3 μg/kg, s.c.. The immunologically reactive insulin in rats decreased after the blood glucose rise. This is probably an α_2-agonist effect as clonidine is reported to do the same in rats and rabbits. It is not known if this rise in blood glucose occurs in dogs and the present clinical profile does not include elevated blood glucose as a significant effect in humans.

Gastrointestinal effects
Dexmedetomidine has been found to increase intestinal transit time in mice, 10 μg/kg s.c..

Ocular effects
The occurrence of keratitis and corneal opacities was observed in both rats and dogs in repeated dose studies. This was attributed to loss of corneal reflexs and drying of the cornea due to α_2 agonist induced reduction of lacrimation and in conjunction with reduced pain sensation because of the sedative/anesthetic/analgesic effects of dexmedetomidine. This was seen to increase in occurrence and in severity as the doses increased and the duration of sedation/anesthesia increased.

Uterine effects
Dexmedetomidine did not affect oxytocin induced uterine contractions *in vitro* at concentrations from 10^{-7} M to $3x10^{-4}$M. This was found in uteri at all stages of the estrus cycle and early and late pregnancy.

##########

PHARMACOKINETICS/TOXICOKINETICS/ADME

[24]

Study Title: Drug Metabolism Report No. 34
Plasma Concentrations of Dexmedetomidine Following Subcutaneous Dosing in Rat

(#186)

Study No: R&D97617
Vol #30, and page #258:
Conducting laboratory and location: Abbott Laboratories: Abbott Park, IL
Date of study initiation: not stated, analysis was October, 1997.
GLP compliance: yes QA- Reports: Yes

Methods:
Dosing: subcutaneous to 8-10 week old rats, 3/sex, in 3 dosage groups; 20, 100 and 500 mcg/kg
Drug, lot#, % purity: dexmedetomidine hydrochloride, Abbott-85499.1, lot# 295260-0-AX
Formulation/vehicle: normal saline
Observations and times: heparinized blood samples obtained from each rat 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours after injection.

Results:

Dose	Sex	$t_{1/2}$ (hr)[0]	Cmax (ng/mL)	Cmax/D	Tmax (hr)	AUC_0. (ng.hr/ml)	AUC/D	CLp (L/hr.kg)
20	M	1.8	1.56(0.76)	92.1(44.8)	0.6(0.4)	3.6(0.6)	209.6(37.1)	4.9(0.9)
	F	2.4	1.01(0.42)	59.8(24.8)	0.8(0.3)	3.3(0.5)	195.6(29.8)	5.2(0.9)
	Mean	2.1	1.29(0.62)	75.9(36.9)	0.7(0.3)	3.4(0.5)	202.6(31.1)	5.0(0.8)
100	M	2.0	9.89(1.35)	116.9(15.9)	0.5(0.0)	23.6(4.7)	338.5(55.3)	3.0(0.5)
	F	2.0	11.40(0.73)	134.8(8.6)	0.7(0.3)	39.1(3.0)	462.5(35.1)	2.2(0.2)
	Mean	2.0	10.65(1.27)	125.9(15.1)	0.6(0.2)	33.9(6.7)	400.5(79.5)	2.6(0.6)
500	M	1.9	65.34(13.15)	154.5(31.1)	0.9(0.6)	227.5(48.1)	537.8(113.6)	1.9(0.4)
	F	2.0	77.84(0.98)	184.0(2.3)	0.5(0.4)	298.8(171.7)	706.3(405.9)	2.1(1.7)
	Mean	2.0	71.59(10.79)	169.3(25.5)	0.7(0.5)	263.1(119.3)	622.0(282.1)	2.0(1.1)

Dose in mcg dexmedetomidine HCl per kg, Sex = M (male. n=3), F (female, n=3) or mean (M/F. n=6).
Units were as follows; Cmax/D= (pg/mL per mcg/kg); AUC/D (pg.hr/ml per mcg/kg).-- harmonic mean

Summary:
Dexmedetomidine hydrochloride was rapidly absorbed after subcutaneous administration, with peak levels in less than an hour. The dose normalized Cmax and AUC increased with dose, indicating non-linear pharmacokinetics with this route of administration. The males had higher AUC than females at the 20 mcg/kg dose (3.6 vs 3.3), but the females AUC was greater than males at 100 mcg/kg dose (39.1 vs 28.6) and at 500 mcg/kg (298.8 vs 227.5) however, the number of animals in the groups, 3/sex, is insufficient to make definitive conclusions. The elimination $t_{1/2}$ was about 2 hours for all doses in both sexes. The Clearance decreased with increasing dose, 5, 2.6 and 2.0 L/hr.kg, for 20, 100 and 500 mcg/kg, respectively.

##########

[25]

Study Title: Pharmacokinetics of ^{3}H-Dexmedetomidine iv and im in the rat (#265)

Study No: BA-92-13
Vol #46, and page #:384
Conducting laboratory and location: [redacted]
Date of study: September 1995

Methods: The subjects were male Sprague Dawley rats, about 300 g, 48 for iv injection and 48 for im injection. Single injection, 2 ug/kg dose.
Drug, lot#, radiolabel and % purity: Medetomidine Hcl, was reacted with tritium gas, the bridge carbon and the methyl group were tritiated, by [redacted] and the dexmedetomidine isomer was separated at [redacted] chiral chromatography. (Lot #?? 2ug/ml, 3.0MBq/ml) The radiochemical purity was [redacted]
Observations and times: Four rats/group were sampled at each time point, 0.83, 0.17, 0.33, 0.50, 0.75, 1, 1.5, 2, 3, 5 and 7 hour postdosing. Blood was collected and brain, livers, kidneys and adrenals were removed.

Results:
The specific radioactivity was apparently too low to get accurate measurements of parent drug. The estimated half-lives were similar to the results of other studies.

In general, the concentration of dexmedetomidine-related radioactivity was higher in the tissues than in the whole blood or plasma. The brain concentrations were 2 to 5x the plasma levels immediately after dosing and were equal to plasma levels by two hours postdosing. Concentrations of radioactivity in the livers, kidney and adrenals was at least an order of magnitude greater than plasma levels.

NDA 21-038

The following tables were copied from the submission (V46/p392-396):

TABLE 265-1:

Pharmacokinetic parameters of dexmedetomidine in rats after the administration of ^{3}H-dexmedetomidine (2 ug/kg) i.v. or i.m. Most values are rough approximations because only two or three points on the curve were available for the graphical estimation of half-lives.

Parameter		i.v.	im	Remarks
C_{max}	(h)	-	0.5	observed
t_{max}	(h)	-	0.33	observed
AUC_{0-inf}	(ng*h/ml)	0.70	0.81	estimate
f	(%)	100	116	estimate
$t_{½lambda}$	(h)	0.4	na	estimate
V_z	(l/kg)	11.5	na	estimate
CL	(ml/min.kg)	47.5	na	estimate
$t_{½}$	(h)	2.8	na	estimate

na = not available

TABLE 265-2.

Graphically estimated half-lives of total radioactivity and the relative availability of radioactivity to rat tissues after intravenous and intramuscular administration of ^{3}H-dexmedetomidine

	Estimated $t_{1/2}$ (h)		$AUC_{(0-7h)}$ (ng equivalents*h/g)		f (%)
	i.v.	i.m.	i.v.	i.m	
whole blood	11.3	4.6	22.3	17.6	79
adrenals	na	na	1145	868	76
liver	9.8	9.3	750	727	97
kidney	2.1	3.0	339	343	101
plasma	6.2	6.1	15.6	13.1	84
brain	3.8	6.1	26.4	24.6	93

na = not available

Summary

The exposure of the liver, kidney and adrenals to dexmedetomidine-related radioactivity, was 34x, 15x and 51x the plasma exposure, respectively, after iv administration, as determined by AUC comparisons. The specific activity of the labeled dexmedetomidine was evidently too low to reliably measure the disposition over time.

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NDA 21-038

[26]

Study Title: Drug Metabolism Report No. 32
Concentrations of Dexmedetomidine Following a Single IV or IM Dose in Dog
(187)

Study No: Protocol # V96-556; R&D/97/615
Vol #30, page #301:
Conducting laboratory and location: Abbott Laboratories, Abbott Park, IL
Date of study initiation: September 1997.
GLP compliance: The assay was done under GLP
QA- Reports Yes (x) for assay and solution concentration; No
Methods: Three groups of beagle dogs were used, 6 to 24 months of age and about 10 kg bodyweight, 3/sex in each group. One group received a single iv slow bolus of 50 µg/kg of dexmedetomidine in the cephalic vein. Another group received an im dose of 50 µg/kg in the thigh muscle and the third group received as similar im injection of a 250 ug/kg of dexmedetomidine.
Drug, lot #295260-0-AX, % purity: = not supplied, stated that Certificate of Analysis provided [redacted] g 305), but not included in report.
Formulation/vehicle: dexmedetomidine hydrochloride was dissolved in normal saline.
Observations and times: Multiple blood samples were taken after administration of dexmedetomidine, 0.1 (iv only), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours postdosing.

Results:
The following tables were extracted from the submission (V30/p307):

Dexmedetomidine Pharmacokinetic Parameters - Dog IV -single dose							
Dose (ug/kg)	Sex	$t_{½}$ (hr)	V_c (L/kg)	V_B (L/kg)	AUC_{0-inf} (ng.hr/ml)	AUC/D	Cl_p (L/hr.kg)
50	male	0.67	0.56	0.91	46.11	1.09	0.9
50	female	0.68	0.27	0.96	44.58	1.05	1.0
50	mean	0.68	0.41	0.93	45.34	1.07	0.9

Dexmedetomidine Pharmacokinetic Parameters - Dog IM - single dose								
Dose (ug/kg)	Sex	$t_{½}$ (hr)	C_{max} (ng/ml)	C_{max}/D	AUC_{0-inf} (ng.hr/ml)	AUC/D	T_{max}	F (%)
50	male	0.91	13.70	0.32	27.74	0.66	0.9	61.2
50	female	0.83	10.38	0.25	23.57	0.56	1.0	52.0
50	mean	0.85	12.04	0.28	25.66	0.61	0.9	56.6

Dexmedetomidine Pharmacokinetic Parameters - Dog IM - single dose								
Dose (ug/kg)	Sex	$t_{½}$ (hr)	C_{max} (ng/ml)	C_{max}/D	AUC_{0-inf} (ng.hr/ml)	AUC/D	T_{max}	F (%)
250	male	1.14	174.8	0.83	426.6	2.02	0.9	188
250	female	1.52	146.2	0.69	430.1	2.03	1.0	190
250	mean	1.31	160.5	0.76	428.4	2.03	0.9	189

Summary:

The elimination of dexmedetomidine after iv administration was rapid, $t_{½}$ = 0.68 hours, after 50 ug/kg dose. The elimination was slower after im administration with $t_{½}$ of 0.85 hours after 50 ug/kg and 1.3 hours after 250 ug/kg. The plasma clearance averaged 0.9 l/hr.kg and the steady state volume of distribution, V_B, was 0.9 L/kg after iv administration of 50 ug/kg.

The pharmacokinetics were not linear after im administration of 50 and 250 ug/kg as the C_{max} and AUC_{0-inf} values increased by factors of 13x and 17x when the dose increased by only 5x.

##

[27]

Study Title: Abbott-85499 Drug Metabolism Report No.49
Effects of Age on the Plasma Concentrations of Dexmedetomidine following Subcutaneous Dosing in Rat

(Suppl N-331;1/2)

Study No:V98-829 ; Report R&D 98/653
Amendment #, Vol #, and page #: [redacted] 1/1, pg 4
Conducting laboratory and location: Toxicology Department; Abbott Laboratories
Date of study: October 1998
Methods: The study group was in male Sprague-Dawley rats; 40 adults, 8 to 10 weeks of age, and 40 juvenile, 3 weeks of age. All rats received a single dexmedetomidine dose of 100 ug/kg by subcutaneous injection. The blood was sampled at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9 and 12 hours postdosing by cardiac puncture in euthanized rats.
Drug, lot#, % purity: Dexmedetomidine HCl (Lot#295260-0) , Certificate of Analysis cited but not submitted.

NDA 21-038

Results: The following table was extracted from the submission (———— ————.

Dose (ug/kg)	Age	$t_{½}$ (hr)	Cmax (ng/ml)	Cmax/D	t_{max} (hr)	AUC_{0-inf} (ng.hr/ml)	AUC/D	Cl_p (L/hr.kg)
100	Adult	1.51	23.8	0.24	0.44	53.5	0.53	1.9
100	Juvenile	0.77	10.8	0.11	0.50	19.9	0.20	5.0

Summary:

The difference in metabolic rates of the adult versus juvenile rats probably accounts for the differences in pK. The shorter $t_{½}$, 0.77 hrs vs 1.5hrs, the lower Cmax, 10.8 ng/ml vs 23.8 in adults and the lower AUC_{0-inf}, 19.9 vs 53.5, all suggest higher metabolic rates. The clearance, Cl_p, decreased with age also, 5 L/hr.kg in juveniles and 1.9 l/hr.kg in adults.

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[28]

Study Title: Abbott-85499 Drug Metabolism Report No.49
Effects of Age on the Plasma Concentrations of Dexmedetomidine following Intravenous Dosing in Dog

(Suppl N-331;#2/2)

Study No: V98-830 Report: R&D/99/002
Amendment #, Vol #, and page #: ———— ————
Conducting laboratory and location: Toxicology Department; Abbott Laboratories
Abbott Park, IL
Date of study: December 1998
Methods: The study group was in male beagle dogs; 4 adults, over 2 years of age, and 4 juvenile, 3-4 months of age. All dogs received a single dexmedetomidine dose of 50 ug/kg by intravenous injection. The blood was sampled at 0.1, 0.25, 0.5, 1, 1.5, 2, 3, 4, and 6 hours postdosing.
Drug, lot#, and % purity: Dexmedetomidine HCl (Lot#295260-0), Certificate of Analysis cited but not submitted.

Results:
The following table was extracted from the submission (IND 32,934, N-331):

Dose (ug/kg)	Age	$t_{½}$ (hr)	V_c (L/kg)	V_B (L/kg)	AUC_{0-inf} (ng.hr/ml)	AUC/D	Cl_p (L/hr.kg)
50	Adult	1.5	0.2	0.8	118.0	2.8	0.4
50	Juvenile	0.7	0.4	1.2	36.6	0.9	1.2

Summary:
The difference in metabolic rates of the adult versus juvenile dogs probably accounts for the differences in pK. The shorter $t_{½}$, 0.7 hrs vs 1.5hrs, and the lower $AUC_{0\text{-}inf}$, 36.6 vs 118, suggest higher metabolic rates. The clearance, Cl_p, decreased with age also, 1.2 L/hr.kg in juveniles and 10.4 l/hr.kg in adults. The dose of 50 µg/kg were administered by iv injections.

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[29]

Study Title: Abbott-85499 Drug Metabolism Report No.5 -
Plasma concentrations of Abbott-85499 (dexmedetomidine) following repeat intrathecal administration in dog (#237)

Study No: Protocol B95-224: Report No. R&D/96/074
Vol #42, and page #237:
Conducting laboratory and location: Abbott Laboratories Division 46; Abbott Park, Il
Date of study: April 1996

Methods:
Dosing: saline and dexmedetomidine hydrochloride were given by intrathecal injection daily for 28 days, doses of 0, 2, 12 and 80 mcg/dog. Nominal normalization as 0.1, 1.2 and 8.0 mcg/kg/day and groups sizes were 5, 3, 3, and 5 dogs per sex, respectively.

Drug, lot#, % purity: Batch TB95-224, purity not reported.

Results:
The following table was extracted from the submission (V42/pg242):

Plasma Dexmedetomidine Pharmacokinetic Parameters after Intrathecal Injection							
Dose[a] (mcg/dog)	Day	sex	C_{max} (pg/ml)	C_{max}/D	$t_{½}$ (hr)	AUC (pg.hr/ml)	AUC/D
2	1	M	7.9	39.7	nf	3.7	18.6

Plasma Dexmedetomidine Pharmacokinetic Parameters after Intrathecal Injection							
Dose[a] (mcg/dog)	Day	sex	C_{max} (pg/ml)	C_{max}/D	$t_{½}$ (hr)	AUC (pg.hr/ml)	AUC/D
		F	9.2	46.1	nf	10.4	51.8
		M/F	8.6	42.9	nf	7.0	35.2
	22	M	11.4	57.0	nf	5.2	25.9
		F	14.0	69.9	nf	12.5	62.7
		M/F	12.7	63.4	nf	8.9	44.3
12	1	M	89.8	74.8	0.57	103.6	86.3
		F	89.2	74.3	0.77	144.9	120
		M/F	89.5	74.6	0.65	124.3	104
	22	M	80.9	67.4	0.67	114.9	95.8
		F	81.6	68.0	0.67	129.4	108
		M/F	81.2	67.7	0.64	122.1	102
80	1	M	928	116	0.85	1610	201
		F	1208	151	0.86	1987	248
		M/F	1068	134	0.86	1799	225
	22	M	946	118	0.82	1659	207
		F	1430	179	0.78	2068	259
		M/F	1188	149	0.80	1864	233

[a] dose in mcg/day of dexmedetomidine hydrochloride by intrathecal injection of 0.5 ml, daily for 28 days - nominal normalization to 0.2, 1.2 and 8.0 mg/kg/day
nf = unable to calculate elimination $t_{½}$ SD in table Vol. 42, pg.242

Summary:

Dexmedetomidine rapidly appeared in the plasma after intrathecal administration and the T_{max} was approximately 30-40 minutes at all doses and on Day 1 and Day 22. The elimination $t_{½}$ was not calculable at the low dose of 0.2 mcg/kg as the readings were near the quantitation limit of 10 pg/ml. The females AUC valuses were higher than the AUCs of males at all doses and times and this was also true for the C_{max} values except for the Day 1 mid dose. However, the dose and volumes were by dog and not by bodyweight. The "nominal normalization" did not correct for

the volume differences and the females were 18% lighter than the males on Day 1. The sex difference may be due to greater relative volume into the intrathecal space, with a corresponding increase in vasculature exposed to the drug solution and thereby increasing the relative absorptive surface.

The peak concentrations and AUC values did not change significantly of Day 22 versus Day 1 and the dose normalized AUC and C_{max} increased with dose, suggesting non-linearity of the pharmacokinetics of dexmedetomidine in the plasma after intrathecal administration.

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[30]

Study Title: Plasma Concentrations of Dexmedetomidine Following Intravenous Dosing in Rabbit

(188)

Study No: R&D/97/616
Vol 31, page 001:
Conducting laboratory and location: Abbott Laboratories, Abbott Park, IL
Date of study initiation: April 1997
QA- Reports: No

Methods: Four female rabbits were dosed by slow iv bolus and blood samples taken at intervals, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9 and 12 hours postdosing.

Dosing: Ear vein, slow bolus iv administration of 96 µg/kg.

Drug, lot#, % purity: dexmedetomidine hydrochloride lot #295260-0-AX

Formulation/vehicle: dexmedetomidine hydrochloride in normal saline, 95.9 mcg/ml

Results:
The pharmacokinetic parameters and results (Vol 31/p6) are in the following table:

Parameter - units	value
Dose (µg/kg, iv)	96

V_c (L/kg)	1.2(0.3)
V_B (L/kg)	6.0(2.3)
Cl_p (L/hr.kg)	2.1 (0.5)
$t_{½}$ (hr)	1.83
AUC_{0-inf} (ng.hr/ml)	40.7 (13.4)
AUC/D	0.50 (0.16)

Summary:

The iv administration of dexmedetomidine was studied in rabbits at the dose of 96 mcg/kg. The pharmacokinetics, plasma concentration profile, fits a biexponential disposition model, characterized by an initial apparent Volume of distribution (V_c= 1.2 L/kg) and the terminal Volume of distribution (V_B = 6 L/kg) and a terminal elimination half-life ($t_{½}$ = 1.8 hrs).

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METABOLISM / EXCRETION

[31]

Study Title:

Abbott-85499 Drug Metabolism Report No.6 -
Metabolism and excretion of [^{3}H]-dexmedetomidine (Abbott-85499) in rats.

(238)

Study No: Protocol V95-031: R&D 196/233
Vol #42, and page #270:
Conducting laboratory and location: Abbott Laboratories Division 46; Abbott Park, IL
Date of study initiation: march 1996
Methods: Sprague Dawley rats, 20/sex, 200-250g from [redacted] and sprague Dawley, 4/sex, 200-250 g [redacted] implanted jugular catheters for serial blood sampling.
Dosing: ^{3}H-dexmedetomidine, 0.02 mg/kg, was injected subcutaneously to 24 rats and to 20 rats intravenously, 40 mcCi/rat. The iv administration was done into the femoral vein during light anesthesia and both sc and iv were divided equally between sexes and 2/sex of the cannulated rats were included in each group. The dose groups were as follows:

Treatment group	Number of rats	Dose (mg/kg)	Route	Samples Collected

T1	2	0.02	iv	urine and feces
T2	4	0.02	sc	urine and feces
T3	4	0.02	iv	Plasma
T4	4	0.02	sc	Plasma
T5	12	0.02	iv	Plasma metabolites
T6	12	0.02	sc	Plasma metabolites
X	4	3.0	sc	urine? 48hrs. unclear

Drug, lot#, radiolabel, and % purity: medetomidine HCl, with tritium on the bridge methyl group, was synthesized [redacted] and the dexmedetomidine isomer was separated at Abbott by chiral chromatography. Lot #50498-ST-113; 80 mcCi/mmol, 331 mcCi/mcg or Lot# 50498-ST-130DUnlabeled dexmedetomidine, Lot #295260-0-AX, was added to the labeled dexmedetomidine HCl to provide a solution of 160 mcCi/ml and 0.02 mg/ml. The radiochemical purity [redacted]
Formulation/vehicle: dexmedetomidine hydrochloride was dissolved in normal saline.
Observations and times: Blood samples were withdrawn from cannulated rats at 0.1, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours post dosing. From groups T5 and T6, 1/sex/group were sacrificed and blood samples extracted by cardiac puncture at 0.5, 1, 2, 6, 12 and 24 hours. The urine and feces samples were collected for groups T1 and T2 for 3 days. There was an additional 4 rats, 2/sex, which received a single 3 mg/kg dose, sc, of tritiated-dexmedetomidine and urine was collected for 48 hours. The treatment group descriptions were not clear.

Results:
Metabolites were isolated from the urine of rats receiving the 3 mg/kg sc dose. After centrifugation and column separation, the samples were analyzed by mass spectrophotometer with some internal standards of expected metabolites. The tritium was stable in the position used as less than 1% of the total was converted to tritiated water in three days. The recovery of radioactivity in feces and urine averaged 98% of the total dose.
There were sex related differences: 1) the AUC for total radioactivity was 1.6 to 2 times greater in females, 2) females excreted more of the radioactive dose in the urine (72%) than males (57%) after iv dosing, 3) the formation of sulfate and mercapturic acid conjugates predominates in females.

However, the iv AUC for dexmedetomidine in the plasma after 20µg/kg were the same in males, 2.59 ngEq.hr/ml, as females, 2.24 ngEq.hr/ml. After sc administration the AUC values for dexmedetomidine were 6.84 for males and 4.23 for females.

A summary table of the distribution of dexmedetomidine and metabolites, percent of total

radioactivity, has been excerpted from the submission (Vol42/pg318):

	Percent Total ^{3}H AUC			
	iv		sc	
Component	Male	Female	Male	Female
Dex.	8.04	4.98	20.36	10.51
COOH	15.71	4.72	9.61	2.19
OH	1.89	1.87	0,66	2.14
G-OH	12.70	6.92	8.36	4.90
SO_3-OH	1.55	18.00	0	13.37
M-2	3.29	2.76	3.20	2.54
M-5	15.78	8.59	11.59	8.25
M-6	21.65	26.76	20.70	26.92
M-7	3.45	7.21	3.90	10.64
M-8	3.85	8.72	5.91	7.51
Others	12.14	9.50	15.71	11.06

Corrected for tritiated water. **Dex** = dexmedetomidine.
COOH = carboxylic acid metabolite (MPV-1306).
OH = hydroxy metabolite (MPV-1305).
G-OH = glucuronic acid conjugate of the hydroxy metabolite.
SO_3-OH = Sulfate conjugate of the hydroxy metabolite.
M-2 to M-8 unidentified metabolites.

Summary:

The metabolism of ^{3}H-dexmedetomidine was studied in fasted Sprague Dawley rats following sc and iv dosing, 0.02 mg/kg. Less than 1% of the total radioactivity was found as tritiated water but the proportion of tritiated water in the plasma slowly increased until by 72 hours it represented 90% of the plasma radioactivity. The total metabolism was extensive as less than 1% was excreted in the urine as parent drug.

The mean dexmedetomidine AUC values after sc administration were 4.23 ng eq.hr/ml for the females versus 6.48 for the males. After iv administration, the females AUC for dexmedetomidine, 2.24ng eq.hr/ml, was about the same as males, 2.59ng eq.hr/ml. The females also appeared to excrete more in the urine than the males, 72% versus 57% respectively after iv administration and 59% versus 41% after sc injection. The total radioactivity recovery was 98% of the dose.

Plasma profiles of metabolites were often common to both sexes, including carboxyl metabolite (COOH), hydroxy metabolite (OH) and its glucuronide (G-OH) and sulfate (SO_3-OH) conjugates. The carboxyl predominated in the males, while the sulfate metabolites were predominant in the females. Also excreted in the urine were unidentified M-2, M-5, M-6, M-7, and M-8.

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NDA 21-038

[32

Study Title: Abbott-85499 Drug Metabolism Report No. 17 - Tissue distribution of radioactivity in rats following a single intravenous 0.02 mg/kg dose of [3H]dexmedetomidine HCl (Abbott-85499.1) (247)

Study No: R&D/96/720
Vol #44, page #1:
Conducting laboratory and location: [redacted]
Abbott Laboratories; Abbott Park, IL
Date of study initiation: April 1996

Methods: 20 male and 20 female Sprague Dawley rats were injected with tritium labeled dexmedetomidine and 4 male Long Evans rats.

Dosing: iv, tail-vein injection of 0.02 mg/kg;

Drug, lot#, radiolabel (if applicable), and % purity: tritiated dexmedetomidine, lot #50498-ST-223; 326.8 mCi/mg; non-labeled dexmedetomidine, lot # 295260-0-/ [redacted]

Formulation/vehicle: dexmedetomidine hydrochloride was dissolved in normal saline

Observations and times: a) 10 time points post administration, 0.25 to 12 hours, 2 rats/sex were sacrificed and the pharmacokinetics were examined. b) 4 Long Evans male rats were also received labeled dexmedetomidine and they were sacrificed at 0.25, 1, 24 or 72 hours post administration.

Results: The tissue/plasma ratios were greater than 1, at least once, for all tissues but bone. The highest plasma concentrations 3.45 ng eq/g in males (0.25hrs) and 5.36 ng eq/mg in females (2hrs). Tritiated water was less than 5% of the plasma from 0.25 to 6 hours. The $t_{1/2}$ of radioactivity was about 40 hours in Sprague Dawley males and 26 hours in females. The pharmacokinetic parameters in various tissues are presented in the following table(V44/pgs 93, 94):

Matrix	terminal $t_{1/2}$ - (hrs)		AUC (ng eq . hrs/g)	
	male	female	male	female
Adrenal	13.9	24.4	8,400	19,020
Blood	48.5	33.4	45.2	93.8
bone (femur)	2.45	2.0	94.7	3.9
brain	26.9	23.6	49.2	74.7
eyes	44.1	33.5	31.9	95.7
heart	29.4	20.0	45.5	69.4
kidneys	16.9	18.6	507	471
small intestine + contents	12.4	11.5	1,120	1,420
liver	15.4	14.3	2,430	1,690
lungs	16.2	18.9	1,230	1,820
muscle (thigh)	35.1	17.9	30.7	49.8
ovaries	-	14.8	-	99.5
testes	11.9	-	513	-

The largest difference with the male Long Evans rats was the $t_{1/2}$ of 36.6 hours in the pigmented eyes and an AUC of 3,970, as compared to the AUC of 31.9 in the non-pigmented eyes of the Sprague Dawley males. The levels of radioactivity were not very different between the skin of the albino rats (7.23 ng eq/g) and that of the pigmented rats (6.92 ng eq/g). The tissues containing the highest percentage of the dose during the first 4 hours were muscle (16-25%), liver (34 to 42%) and small intestine with contents (22 to 24%).

The majority of the tritiated dexmedetomidine was excreted in the urine by the Sprague Dawley rats of both sexes. Within 24 hours post-dosing, the males had excreted 52 to 62% of the dose in urine and 23 to 27% in the feces. The females excreted 65% to 74% in the urine and 14% to 18% in the feces. The recoveries were from 90.7 to 101% of the dose and tritiated water accounted for 3.1% at 24 hrs and 8.3% at 72 hours. At 72 hour post, except for the adrenals (28.1 ng eq/g in males and 58.3 in females), the blood and all tissues had levels less than 1 ng eq/g. "By 72 hours, <2% of the dose was associated with any of the tissues analyzed."

Maximum tissue concentrations are presented in the following table:

Tissue	C_{max} (ng.eq/g)	
	male	female
liver	264	233
blood	2.9	3.6
Adrenals	245	452
lungs	216	272
kidneys	152	109
small intestine + contents	150	185
large intestine + contents	133	74
stomach + contents	90	125
pancreas	77	92
brain	26	27

Summary:

The presence of dexmedetomidine in the eye of pigmented rats was 28 times the concentrations in the albino rats and suggest binding to melanin. However the labeled compounds retained in the skin of pigmented male rats was not greater than in the skin of the albino males. The highest concentrations were seen in the liver and adrenals and the C_{max} in the liver, lungs and adrenals is almost 2 orders of magnitude greater than the peak blood levels. The excretion was nearly complete by 72 hours except for the adrenals which still had 28 to 58 ng eq/g in males and females respectively. The exposure of various tissues to labeled compound exceeded the plasma exposure, as determined by AUC ratios. In the males, the exposure ratios were 185x, 54x and 11x, for adrenals, liver and kidneys, respectively.

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NDA 21-038

[33]

Study Title: Abbott-85499 Drug Metabolism Report No. 11 -
Metabolism and excretion of [^{3}H]-dexmedetomidine following intravenous or subcutaneous administration to chronically bile duct cannulated rats
(#261)

Study No: Protocol V96-014: R&D196/443
Vol #45, page #221:
Conducting laboratory and location: Abbott Laboratories Division 46: Abbott Park, IL
Date of study initiation: March 1996
GLP compliance: not stated
QA- Reports Yes ( ) No (x):

Methods: Sprague Dawley rats, 4/sex, implanted with chronic bile duct cannula were used to determine the excretory pattern and an additional cannulated rats, one female and 2 males, were used for metabolite identification.
Dosing: For excretory pattern determination, 2 rats/sex were injected iv with labeled dexmedetomidine, 0.02 mg/kg (approx. 40 mcCi/rat) and immediately a solution of taurocholic acid in saline (27.8mg/ml) was infused into the distal end of the bile duct cannula at the rate of 1 ml/hr, for 24 hours. The remaining 2/sex received labeled dexmedetomidine, 0.02 mg/kg, by subcutaneous injection and bile duct infusion was as previously described. The rats used for metabolite determination were injected by the appropriate route with a single dose of 2.75 mg/kg, 40 mcCi/rat.

Drug, lot#, radiolabel (if applicable), and % purity: Medetomidine HCl, with tritium on the bridge methyl group, was synthesized by Amersham and the dexmedetomidine isomer was separated at Abbott by chiral chromatography. (Lot #50498-ST-157D; 80 mcCi/mmol) Unlabeled dexmedetomidine, Lot #295260-0-AX, was added to the labeled dexmedetomidine HCl to provide a solution of 160 mcCi/ml and 0.02 mg/ml. The radiochemical purity was

Formulation/vehicle: dexmedetomidine was dissolved in normal saline.
Observations and times: Bile was collected from 0 to 2 , 2 to 4, 4 to 6 and 6 to 24 hours postdosing. Urine and feces were collected at 24 hours. Bile samples used for metabolite isolation were collected at 3, 6 and 24 hours.

Results:
The recovery of radioactivity in the bile over 24 hours amounted to a mean of 52% of the total dose after iv administration and 45% after sc administration. Urinary excretion accounted for 41% of the dose after iv injection and 37% after sc administration. Total recovery was between 83% and 97%. Parent dexmedetomidine was present in bile from 0 to 0.1% of dose, indicating

extensive metabolism. The major metabolite in the bile was the glucuronide of the hydroxylated metabolite (G-OH), 14-16% of iv dose and 12 to 18% of sc dose. An unidentified conjugate, M-2, represented 5.6% to 9.9% after iv and sc dosing, respectively. The carboxyl metabolite (COOH) and mercapturic acid conjugate (M-OH) represented 0 to 1.3% of the dose. The sulfate (SO_3-OH) and glutathione (GS-OH) conjugates were 3 to 6 fold higher in females, but only represented 3.9 and 2.7% of the dose in females, iv and sc, and 1.3 and 0.85% in males, iv and sc, respectively. Unidentified metabolites represented 12 to 18% of the dose.
The urine metabolic pattern was similar to the bile and unchanged dexmedetomidine only represented 0.4% to 1.1% of the dose. The proposed metabolic pathway was presented previously and is primarily initiated by 3-methyl hydroxylation and subsequent oxidation or conjugation with sulfate, glucuronide, glutathione, or mercaturate.

Summary:

The major metabolite in the bile and urine was the glucuronide of the hydroxylated dexmedetomidine and the carboxyl metabolite was also a major excretory product. The number of animals/sex was only 2 and because there was differences of three to five fold between subjects, the comparison of group means is not accurate. However, in general terms, the bile represented about 50% of the labeled dose by iv and by sc routes and urine represented about 30% of the labeled dose. The metabolites were qualitatively the same, iv versus sc. with some differences in percentage. This was also true of any sex differences.

##

[34]

Study Title: Abbott-85499 Drug Metabolism Report No.28
Metabolism of [^{3}H]dexmedetomidine, [^{3}H]levomedetomidine and[^{3}H]medetomidine by precision-cut rat liver slice (#250)

Study No: Report No. R&D/971504
Vol #44, page #245:
Conducting laboratory and location: Abbott Laboratories Division 46: Abbott Park, IL
Date of study report: November 1997.
GLP compliance: no

Methods:

Drug, lot#, radiolabel, and % purity: Medetomidine HCl (lot #TRQ-7319), with tritium on the bridge methyl group, was synthesized by Amersham and the dexmedetomidine (Lot #50498-ST-108A; 80 mcCi/mmol) and levomedetomidine (Lot #50498-ST-108B; 80 mcCi/mmol) isomers were separated at Abbott by chiral chromatography. Unlabeled dexmedetomidine (Batch 002), levomedetomidine (Batch PT0202) and medetomidine (Batch TT4651) were added to the labeled compounds to provide a solution of 3.33 mcCi/ml in 25% aqueous ethanol.

medetomidine.

Results:

The *in vitro* results were similar to *in vivo* results as dexmedetomidine was metabolized by both oxidation (OH and COOH) and conjugation (SO_3OH, GS-OH, G-OH, M-OH). The conjugates were nearly all of the hydroxylated dexmedetomidine although there were traces of the N-glucuronide and about 25% of the dexmedetomidine metabolites were unknown. Greater than 70% of levomedetomidine and medetomidine metabolites were unidentified. The following table was copied from the submission(V44/p262):

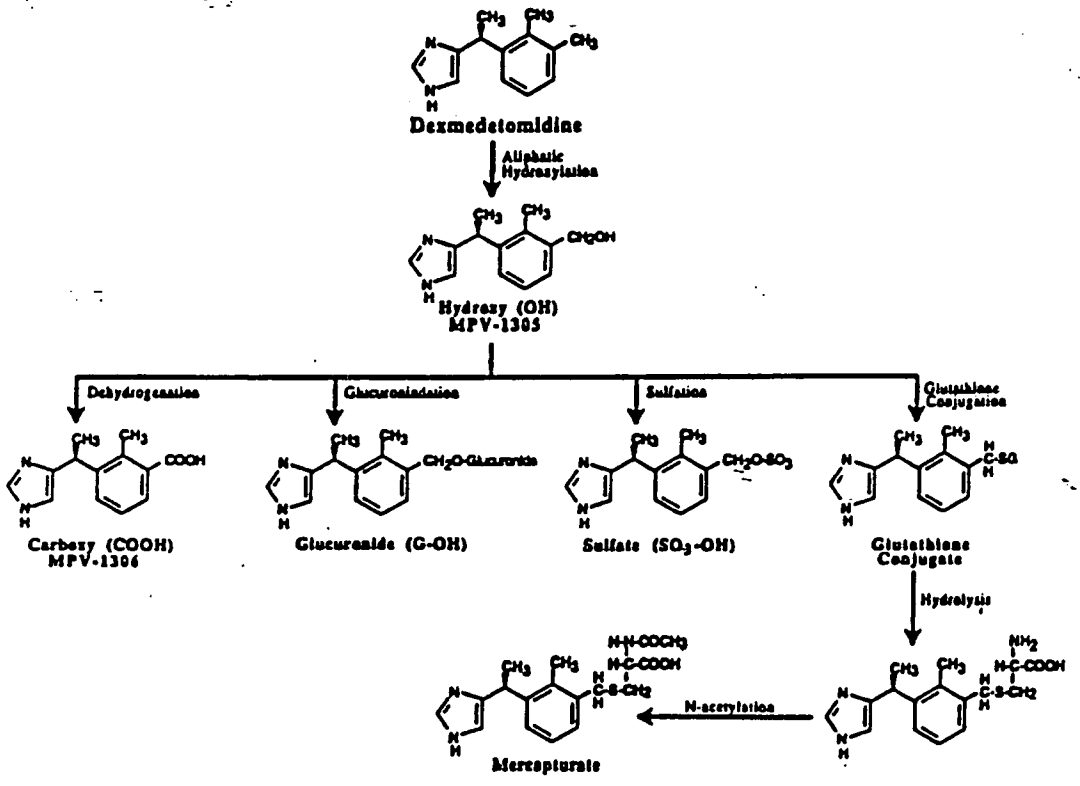
Mean Distribution of Metabolites after Incubation of
[^{3}H]Medetomidine, [^{3}H]Dexmedetomidine and [^{3}H]Levomedetomidine
with Male and Female Rat Liver Slices

	% Total Metabolites					
Metabolite	Medetomidine		Dexmedetomidine		Levomedetomidine	
	(M) (n=2)	(F) (n=1)	(M) (n=3)	(F) (n=2)	(M) (n=2)	(F) (n=1)
G-Dex 1	t	t	t	t	t	t
G-Dex-2	t	t	t	t	t	t
G-Levo	nd	nd	nd	nd	nd	nd
COOH	5.84	0.87	15.44	2.15	2.75	1.43
OH	5.78	5.35	11.67	8.07	4.98	8.02
G-OH	20.77	2.94	37.59	6.32	16.35	6.12
SO_3OH	3.99	7.49	6.73	30.57	6.12	11.78
MOH	1.63	2.01	2.52	10.44	nd	nd
GS-OH	0.54	2.64	2.15	8.58	nd	0.71
N-Methyl	t	t	t	t	t	t
H-1	nd	nd	nd	nd	nd	nd
Others	61.46	78.70	23.89	33.88	69.81	71.94
Turnover(%)	48.66	30.22	80.76	41.61	62.37	18.94

G-Dex-1 = N-glucuronide of dexmedetomidine
G-Dex-2 = N-glucuronide of dexmedetomidine
G-Levo = N-glucuronide of levomedetomidine
COOH = carboxylic acid metabolite (MPV-1306)
OH = hydroxy metabolite (MPV- 1305)
G-OH = O-glucuronide of the hydroxy metabolite
SO_3OH = sulfate conjugate of the hydroxy metabolite
M-OH = mercapturic acid conjugate of the hydroxy metabolite
GS-OH = glutathione conjugate of the hydroxy metabolite
N-methyl = N-methylated metabolite (MPV-1709)
H-1 = glucuronide of die hydroxylated N-methyl metabolite
Turnover = % drug converted to metabolites
t = trace nd = not detected

The major dexmedetomidine metabolites from male rat liver slices were the 3-hydroxy, the carboxyl and the vast majority as the glucuronide of the 3-hydroxy dexmedetomidine. The sulfate, glutathione and mercapturic conjugates were minor in the males, but were the major metabolites from the female rat livers. The metabolism of levomedetomidine and medetomidine was qualitatively similar to dexmedetomidine with less of a difference in sex-linked metabolism. The following diagram of proposed metabolism was copied from the submission (V44/p269):

Proposed Metabolic Pathway for [3H]Dexmedetomidine in Rats



Summary:

The metabolism by rat livers of dexmedetomidine, levomedetomidine and the racemate m-edetomidine was studied *in vitro*. The hydroxlyation appears to be the major first step and with dexmedetomidine, the males livers appear to preferentially glucuronidate this hydroxyl and the carboxyl metabolite while the livers from female rats preferentially make sulfate, mercapturic and glutathione conjugates of the hydroxy dexmedetomidine. The latter conjugates were minor

metabolic products in the males. The metabolism of the racemate and the levo isomer of dexmedetomidine were qualitatively similar.

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[35]

Study Title: Abbott-85499 Drug Metabolism Report No.19 - Metabolism and disposition of [^{3}H]Abbott-55499. I (dexmedetomidine HCl) following subcutaneous and intravenous administration to dogs (#240)

Study No: Protocol V96-020; Report No. R&D/97/291
Vol #42, page #367:
Conducting laboratory and location: Abbott Laboratories Division 46
Methods: Dogs were injected with labeled dexmedetomidine iv and a week later sc. The urine and feces were extracted for labeled metabolites and an enzymatic hydrolysis of the urine samples to evaluate glucuronides and sulfate conjugates.
Dosing: Two beagle dogs/sex, 8-12kg, 0.5 to 3 years of age. The injections were in the cephalic vein, 0.02 mg/kg of labeled dexmedetomidine, approximately 50 mcCi. The blood was sampled and the urine and feces were collected for 5 days. One week after the initial iv injection, the dogs were injected sc with the labeled dexmedetomidine at 0.02 mg/kg and the blood sampling and urine and feces collection was repeated.
Drug, lot#, radiolabel, and % purity: Medetomidine HCl, with tritium on the bridge methyl group, was synthesized by Amersham and the dexmedetomidine isomer was separated at Abbott by chiral chromatography. (Lot #50498-ST-223; 80 mcCi/mmol) Unlabeled dexmedetomidine, Lot #295260-0-AX, was added to the labeled dexmedetomidine HCl to provide a solution of 20 mcCi/ml and 0.08 mg/ml.
Formulation/vehicle: normal saline was used as solvent.
Observations and times: The blood samples after dexmedetomidine administration were at 0, 0.1, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24,48, 72, 96 and 120 hour postdosing. The urine was collected in 0-24 hr, 24-48 hr and pooled by volume for a representative 0-48hr sample. The feces samples for 0-24hrs and 24-49 hrs were extracted and analyzed. An average of 63% of the radioactivity was extracted.

Results:
The tritiated water comprised less than 1% of the total tritium label but the percent of the radioactivity in the plasma constituting tritiated water increased with time and by 120 hours postdosing, it was 74% of the plasma radioactivity.

There were no apparent sex-related differences in metabolic profile. A comparison of AUC_{0-120} was 110.4 ng Eq.hr/ml after sc administration and 101.8 ng Eq.hr/ml after iv administration, supporting good bioavailability. The peak plasma levels of labeled dexmedetomidine occurred

about 2 hours after sc administration (4.39 ng Eq/ml) and the peak level of radioactivity occurred with 6 hours of sc dosing (8.98 ng Eq/ml). Radioactivity was excreted mainly in the urine (>80%) by both routes of administration and in both sexes. The fecal excretion amounted to about 13%.

The following tables were taken from the submission (V42/pg384,386) and present the metabolite distribution:

Plasma Metabolite Distribution

Plasma Component *	%AUC ^{3}H Intravenous	Subcutaneous
Total ^{3}H	100.00	100.00
Dex	21.47	24.48
COOH	7.09	5.89
SO_3OH	10.21	9.87
G-OH	11.88	7.64
OH	1.43	1.28
D-2	4.54	3.81
D-4	9.68	7.73
D-6	5.57	5.22
D-7	1.75	4.45
Others	26.38	29.65

**corrected for tritiated water*

Urine Metabolite Distribution

Urine Component	% ^{3}H-Dose Intravenous	Subcutaneous
COOH	13.21	11.77
SO_3OH	13.12	15.25
G-OH	10.81	8.06
OH	1.32	2.21
D-1	9.00	9.88
D-2	7.52	6.76
D-3	6.12	6.60
D-4	6.31	6.29
D-6	1.91	2.46
Dex.	0.00	0.43
Others	9.65	10.80
% Dose Excreted	78.97	80.51

Summary:

The bioavailability of tritiated dexmedetomidine, in dogs, by sc injection was comparable to iv dosing and there was no sex differences observed in metabolic profiles. The exposures to the parent drug accounted for 21 to 25% of the AUC of total radioactivity. The plasma metabolites included carboxyl and hydroxy metabolites with the glucuronides and sulfate conjugates of the latter.

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NDA 21-038

[36]

Study Title: Abbott-85499 Drug Metabolism Report No.25 - Metabolism of [^{3}H]dexmedetomidine, [^{3}H] levomedetomidine and [^{3}H]medetomidine by precision-cut dog liver slices (#251)

Study No: Report No. R&D/97/454
Vol #45, and page #001:
Conducting laboratory and location: Abbott Laboratories Division 46: Abbott Park, IL
Date of study report: August 1997

Methods: One female and two male beagles dogs, about 10 kg body weight, were used in the experiment. Livers were placed in Krebs-Henseleit buffer, 8mm biopsy punch for sample. Sample sliced to 250 microns thickness and placed in glass ———] vials with oxygenated Krebs-Henseleit buffer at 37°C and buffer containing the labeled compounds were added for final concentrations of 10mcM. After incubation for various times, the reactions were stopped by freezing and the metabolic profile was determined by LC/MS or LC/MS/MS.

Drug, lot#, radiolabel, and % purity: Medetomidine HCl, with tritium on the bridge methyl group, was synthesized by ——— l the dexmedetomidine isomer was separated at Abbott by chiral chromatography. (Lot #50498-ST-223; 80 mcCi/mmol) Unlabeled dexmedetomidine, Lot #295260-0-AX, was added to the labeled dexmedetomidine HCl to provide a solution of 20 mcCi/ml and 0.08 mg/ml. ———

Results:
The metabolism of dexmedetomidine appears to involve N-methylation in about 50% of the metabolites. The 3-hydroxy and related hydroxy compounds account for about 27% of the metabolites and there is some oxidation/conjugation of the parent compound. Although the N-methyl compound can be demethylated by the P450s, this does not appear to be a major pathway in the dog. The N-methyl is excreted as its hydroxylate and various conjugations of the hydroxylated methyl. N-glucuronidation, a major pathway in human liver metabolism of dexmedetomidine, does not appear to have a significant role in metabolism by the dog liver.

The metabolism of levomedetomidine appears qualitatively similar to that of dexmedetomidine. The N-methyl and related compounds accounted for 37% of the metabolites and the direct N-glucurinidation was a significant route and accounting for 16% of the metabolites. The following table was copied from the submission (V45/p17):

NDA 21-038

Mean Distribution of Metabolites after Incubation of [^{3}H]Medetomidine, [^{3}H]Dexmedetomidine and [^{3}H)Levomedetomidine with Dog Liver Slices

Metabolite	% Total Metabolites Medetomidine (n=1)	Dexmedetomidine (n=3)	Levomedetomidine (n=1)
G-Dex- I	t	t	t
G-Dex-2	t	t	t
G-Levo	18.56	t	16.42
OH	5.11	6.28	2.58
G-OH	2.91	11.77	0.78
SO_3OH	1.29	3.38	1.60
COOH	0.47	5.38	nd
N-Meth	32.71	9.71	30.89
N-Meth-OH	3.52	4.57	3.60
N-Meth-G-OH	2.69	10.61	1.44
N-Meth-SO_3OH	3.85	18.39	1.17
N-Meth-COOH	nd	6.78	0.32
H-3	8.56	4.95	15.80
Others	20.34	18.18	25.40
Turnover (%)	71.88	91.96	74.37

G-Dex- 1, G-Dex-2 N-glucuronide conjugates of dexmedetomidine
G-Levo = N-glucuronide conjugate of levomedetomidine
OH = hydroxy metabolite (MPV-1306)
G-OH glucuronide conjugate of the hydroxy metabolite
SO_3OH = sulfate conjugate of the hydroxy metabolite
COOH carboxylic acid metabolite (MPV-1305)
N-Meth = N-methylated metabolite (MPV-1709)
N-Meth-OH N-methyl hydroxy metabolite
N-Meth-G-OH = glucuronide of the N-Methyl hydroxy metabolite
N-Meth-SO_3OH = sulfate conjugate of the N-methyl hydroxy metabolite
N-MCth.COOH = N-methyl carboxylic acid metabolite
H-3 = unidentified metabolite
Turnover = % parent drug converted to metabolites
nd = not detected t = trace

Summary

The in vitro metabolism of dexmedetomidine by dog livers was mainly by N-methylation with additional hydroxylation or carboxylation. These metabolites in addition to the sulfate and glucuronide conjugates of the N-methyl hydroxy, accounted for 50% of the metabolism. The 3-hydroxy and its sulfate and glucuronide conjugates accounted for an additional 37% of the metabolism. The sponsor states no sex difference was apparent, however, no tabulation of comparative results were provided.

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NDA 21-038

[37]

Study Title: Abbott-85499 Drug Metabolism Report No.26 - Phase 1 study of the metabolism and excretion of [^{3}H]dexmedetomidine HCl (Abbott-85499.1) in normal male subjects (Protocol Dex-96-018). (#241)

Study No: DEX-96-018; Report No. R&D/97/457
Vol #43, page #001:
Conducting laboratory and location: Abbott Laboratories Division 46: Abbott Park, IL
Date of study: December 1997
GLP compliance: not stated
QA- Reports: No (x):

Methods: A single intravenous injection of label dexmedetomidine was given to five healthy male subjects, 2 ug/kg, about 0.5 mCi. One of the subjects was a slow metabolizer of dextromethorphan, suggesting CPY2D6 deficiency. Blood samples were taken 5, 7, 15, 20, 30 and 45 minutes postdosing and 1, 1.5, 2, 3, 4, 5, 6 ,8 12, 24, 48, 72, 96, 168, 192, 213 and 554 hours postdosing.

Urine was collected over intervals of 0-2, 2-4, 4-6, 6-8, 8-10, 10-12 and 12-24 hours postdosing. Composite samples of 24, 24-36 and 36-48 hours postdosing were analyzed and then daily collections. Feces were collected daily for nine days after dosing.

Drug, lot#, radiolabel, and % purity: Medetomidine HCl, with tritium on the bridge methyl group, was synthesized [redacted] and the dexmedetomidine isomer was separated at Abbott by chiral chromatography. (Lot #55585-ST-37; 6.04 mcCi in 9ml ethanol) Unlabeled dexmedetomidine, Lot #15-096VH, was added to the labeled dexmedetomidine HCl to provide a solution of 8.028 ug/g, 30.27 uCi/g dose solution. The radiochemical purity [redacted]

Results:
The pattern of radioactivity was similar in all subjects, decreasing from a mean of 3.18 ng Eq/g at 10 minutes to 1.51 ng Eq/g at 30 minutes and slowly rising again to 2.02 ng Eq/g at 2 hours. This rise was primarily due to the increase in the N-glucuronides in the plasma. The levels of radioactivity gradually fell until a slight rise was seen at 5 hours, probably due to enterohepatic recirculation. The plasma levels then gradually decreased over the total of nine days and traces were observed on Day 24. The $t_{½}$ for plasma tritium was 10.75 days and for tritiated water, 9.46 days. In the initial 24 hours, about 85% of the dose was recovered in the urine. The total recoveries averaged 99.25% (98.62 - 101%). The urinary excretion accounted for a total of 95% and the feces 4% of the dose in 9 days. The pharmacokinetic parameters are presented in the following table copied from the submission (V43/p27+):

Table 241-1:

Dexmedetomidine Pharmacokinetic Parameters

Parameter	Study No. Dex-96-018	Subjects 2-6 BA-91-04	Subject 1 BA-91-04
Cmax (ng/g)	3.12 ± 0.27#	2.99 ± 0.68	3.12
$t_{1/2}$ (h)*	2.85 ± 1.10'	2.62 ± 0.46	7.29
AUC_{0-inf} (ng.h/g)	3.49 ± 0.68'	2.94 ± 0.47	5.78
CL (L/h)	42.60 ± 7.10,	38.44 ± 5.75	18.20
V_{ss} (L)	143.9 ± 15.50'	125.80 ± 15.19	177.00
V_B(L)	182.1 ± 36.0'		

* Harmonic mean. where applicable
# (n) = 5
' (n) = 3

The results are compared to a previous study, BA-91-04 (#252, below) with uniabeled dexmedetomidine, and are in agreement when the slow metabolizer, #1, was removed. The results agree very well and indicate a two compartment model.

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Table 241-2:

[^{3}H]Dexmedetomidine Human Metabolites
(Mean Values)

Component	Plasma *	Urine#	Feces#
Dexmedetomidine	14.70	nd	0.06
G-Dex- 1	35.20	19.56	0.09
G-Dex-2	6.17	14.43	0.01
OH	nd	1.11	0.18
G-OH	3.02	7.66	0.04
COOH	1.10	4.80	0.47
N-Methyl	0.29	nd	nd
H-1	20.55	14.51	0.19
H-2	2.47	nd	nd
H-3	10.45	nd	0.04
H-4	0.33	3.76	nd
Others	5.78	28.02	2.29

* % AUC for total plasma radioactivity
# % of the dose
nd = not detected

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Table 241-3:

Summary of the Distribution of Metabolites in 0-72 Hour Human Urine following a Ten Minute Infusion of [^{3}H] Dexmedetomidine.HCl (2 ug/kg)

	Urine Sample(h)/% ^{3}H-Dose						
Metabolite	H101	H102	H103	H104	H105	Mean	SD
Dexmedetomidine	nd	nd	nd	nd	nd	0.00	0.00
G-Dex1	16.10	24.00	21.07	19.04	17.57	19.56	3.09
G-Dex2	13.66	18.25	14.72	14.19	11.36	14.43	2.49
OH	1.35	0.67	1.36	1.05	1.11	1.11	0.28
G-OH	8.35	8.15	6.88	7.11	7.79	7.66	0.64
COOH	6.01	3.60	4.02	5.17	5.20	4.80	0.98
H-1	16.36	14.86	12.43	15.27	13.61	14.51	1.52
H-4	4.56	3.08	3.11	3.94	4.10	3.76	0.65
Others	29.53	20.42	28.02	28.53	33.58	28.02	4.77
% Dose Excreted	95.92	93.03	91.61	94.30	94.31	93.83	1.61

G-Dexl and G-Dex2 = N-glucuronide conjugates of parent drug
COOH = carboxylic acid metabolite (MPV~1306)
OH = hydroxylated metabolite (MPV 1305)
G-OH = glucuronide conjugate of the hydroxy metabolite
H-1 = N-methylated glucuronide conjugate of the hydroxy metabolite
H-4 = N-methylated carboxylic acid metabolite
n d = not detected

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Table 242-4:

Summary of the Distribution of Metabolites in Human Feces following a Ten Minute Infusion of [^{3}H]Dexmedetomidine HCl (2 *ug/kg)*

	Fecal Sample % ^{3}H-Dose*						
Metabolite	H101 59&77h	H102 25&28h	H103 24&99h	H104 57&72h	H105 57&78h	Mean	SD
Dexmedetomidine	nd	0.10	0.14	nd	0.07	0.06	0.06
COOH	0.50	0.38	0.36	0.61	0.52	0.47	0.10
OH	0.17	0.29	0.44	0.02	nd	0.18	0.19
G-OH	nd	0.01	nd	0.11	nd	0.04	0.06
G-Dexl	nd	0.20	0.17	nd	0.06	0.09	0.10
G-Dex2	nd	0.03	nd	nd	nd	0.01	0.01
H-I	0.17	0.26	0.22	0.08	0.25	0.19	0.07
H-3	0.04	0.06	0.08	0.02	0.00	0.04	0.03
Others	2.45	2.12	2.81	1.69	2.39	2.29	0.42
% Dose Excreted	3.32	3.54	4.22	2.53	3.29	3.33	0.61

G-Dex1 and G-Dex2 = N-glucuronide conjugates of parent drug
COOH = carboxylic acid metabolite (MPV-1306)
OH = hydroxylated metabolite (MPV-1305) H-1 = N-methylated glucuronide conjugate of the hydroxy metabolite G-OH = glucuronide conjugate of the hydroxy metabolite
H-3 = uncharactetized metabolite nd = not detected
* Total percent of dose excreted for each individual at timepoints listed

Summary:

The pharmacokinetics of labeled dexmedetomidine in man after a 10 minute iv infusion demonstrated a plasma t½ of less than 3 hours and a volume of distribution of about 40L. The comparison of radioactivity and dexmedetomidine $AUC_{0\text{-}24hr}$ indicated that 14.7% of the plasma AUC was represented by the parent compound and 41% of the circulating metabolites were the N-glucuronides. The N-methylated glucuronide of the 3-hydroxylated parent (H-1) was 20.6% of the dose and the only other metabolite in the plasma representing more than 6% of the radioactivity was unidentified, H-3.

The parent compound was not detected in the urine and less than 0.1% of the total dose in the feces, indicating extensive metabolism. The N-glucuronides in the urine represented 33% of the dose given and the urinary H-1 glucuronide represented 14.5% of the dose. The 3-hydroxylated metabolite was 6.7%; the 3-carboxylate was 4.8% and 3.8% was the glucuronide of the N-methylatd carboxylate. The unidentified urinary metabolites represented 28% of the administered dose. (Metabolic Pathways: page 72 (rat), page 100 (human))

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[38]

Study Title: Pharmacokinetics and metabolic profiling of ^{3}H-labeled dexmedetomidine in healthy in male volunteers. Biometrical report

(#262)

Study No: Study BA-91 -04 (PBR-9 10208-4)
Vol #46, page #001:
Conducting laboratory and location: [redacted]
Date of study initiation: March 1994
Methods: Human males, 6, healthy volunteers, 18-50 yrs of age
Dosing: 2ug/kg labeled dexmedetomidine by iv infusion over 5 minutes.
Drug, lot#, radiolabel, and % purity:
Observations and times: blood samples taken 0, 5, 7, 10, 15, 20, 30 and 45 minutes, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours after start of infusion. Urine collected 02, 2-4, 4-6, 8-10, 10-12, 12-24, 24-36, 36-48 and 48-72 hours after infusion. Feces = 4 samples per subject.

Results:
The study has limited utility as the pharmacokinetics of the radioactivity was the measure and the half-life of 189 hours is representative of the parent and all the metabolites, including tritiated water. The table is copied from the submission (Vol 46/pg 14):

NDA 21-038

Table 262-1:

dexmedetomidine

	actual dose (nmol) administered	t½ (h)	AUC_0.inf (nmoleq/.L..h)	Cl (L/.h.kg)	Varea (L/.kg)	recovery from urine (%)	recovery from feces (%)	total recovery (%)
mean (n-6)	566.2	189	210.3	0.038	10.41	88.84	5.86	94.70
SD	37.3	20	36.2	0.005	1.93	5.42	1.44	4.25

Summary

The pK of the parent and all metabolites has limited use. The major finding was that approximately 89% of the excreted metabolites are in the urine and only 6% in the feces. The dose of 2ug/kg was sedative and the subjects slept a mean of 1.5 hours after injection.

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[39]

Study Title: Pharmacokinetics and metabolic profiling of ^{3}H-labeled dexmedetomidine in healthy male volunteers. Metabolite profile of ^{3}H-dexmedetomidine in human urine. (#252)

Study No: Study BA-91-04 (PBR-910208-4) [DNO JSS95051]
Vol #45, and page #039:
Conducting laboratory and location: [redacted]

Date of study report: January 1996

Methods: Six male volunteers received an iv dose of 2 mcg/kg labeled dexmedetomidine solution. Blood , urine and feces samples were collected. The urine profile was studied by [redacted] of extracts and the conjugates were separated by enzymatic hydrolysis.

Drug, lot#, radiolabel, and % purity: Medetomidine HCl, with tritium on the bridge methyl group, was synthesized by [redacted] JK) and the dexmedetomidine isomer was separated by chiral chromatography. The catalytic hydrogenation of the double bond in tritium gas resulted in a double labeled medetomidine with high specific activity (1600GBq/mmol). Uniabeled dexmedetomidine was added to the labeled dexmedetomidine HCl to provide a final dosing solution of 3.39MBq/ml and 0.0228 mg/ml.

Results:
The average total recovery of radioactivity was 94.7% and most of the elimination was on the first day with 77.2% in the urine. The reference compounds were two hydroxylated (one = 3-

hydroxy dexmedetomidine) metabolites and one carboxylated (3-methoxy dexmedetomidine) and did not coelute with the three major metabolites in the urine of the 5 volunteers with similar metabolic profiles. The sixth volunteer had a major portion of their metabolism as the hydroxylated dexmedetomidine and its glucuronide conjugate. In this subject the major metabolites of the others were only minor. These result were not presented as tables, only in the summary.

Summary:

The only data provided was in the discussions and it appears that 5/6 volunteer males had similar in vivo metabolism of labeled dexmedetomidine and their principal metabolites were not the hydroxylated or carboxylated dexmedetomidine or their sulfate or glucuronide conjugates. The sixth volunteer did excrete a majority of hydroxylated dexmedetomidine and its glucuronide conjugate. The majority of iv radiolabeled was excreted in the urine (77.2%) and the total recovery was 94.7% of total injected.

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[40]

Study Title: Abbott-85499 Drug Metabolism Report No.23 - Metabolism of [^{3}H]dexmedetomidine, [^{3}H]levomedetomidine and [^{3}H]medetomidine by precision-cut human liver slices (#253)

Study No: Report No. R&D/97/389
Vol #45, and page #065:
Conducting laboratory and location: Abbott Laboratories Division 46: Abbott Park, IL
Date of study report: July 1997

Methods:
Human Liver Slices: The human livers of transplant quality were obtained

Human Liver Microsomes: The human livers of transplant quality were obtained from [redacted]. The liver tissue samples were from 21 subjects and received within 24 hrs of removal. The tissue was homogenized, centrifuged and the microsomal pellets resuspended in phosphate buffer and stored at -70°C until use in incubations for studies. The microsome incubations with medetomidine and isomers was stopped, centrifuged and the supernatants analyzed [redacted]

Drug, lot#, radiolabel, and % purity: Medetomidine HCl (lot #TRQ-7319), with tritium on the bridge methyl group, was synthesized [redacted] and the dexmedetomidine (Lot #50498-ST-108A; 80 mcCi/mmol) and levomedetomidine (Lot #50498-ST-108B; 80 mcCi/mmol) isomers were separated at Abbott by chiral chromatography. Unlabeled dexmedetomidine (Batch 002), levomedetomidine (Batch PT0202) and medetomidine (Batch TT4651) were added to the labeled compounds to provide a solution of 3.33 mcCi/ml in 25% aqueous ethanol. The radiochemical purity was [redacted] medetomidine.

Results:
The metabolism of dexmedetomidine by human liver slices indicates that direct N-glucuronidation is a significant metabolic route. The glucuronidation of the nitrogens represents 37% of the total metabolites. The 3-hydroxylation (10.81%) and N-methylation (10.77%) are also major pathways. The glucuronide conjugate of the hydroxy dexmedetomidine (1.56%), the caboxyl metabolite (1.02%) and the glucuronidation of the N-methyl dexmedetomidine (H-1 = 1.54%) are all minor metabolic pathways. These cited metabolites account for 63% of the total and the remaining 37% have not been identified (See Table 253-1).
The microsomal metabolism of dexmedetomidine indicated that the N-glucuronidation is very variable between humans (20 fold) but the ratio of the the two nitrogens being glucuronidated is relatively constant, suggesting the same enzyme for both sites (See Table 253-2). The Table 253-3, provides pharmacokinetic calculations that indicate that the glucuronidation of two nitrogens differ more in the Vmax than the Km.

The direct N-glucuronidation of dexmedetomidine was a significant route of metabolism, 37% , and with levomedetomidine it was the major pathway, 71.3%. The metabolism of the racemate, medetomidine, was qualitatively similar to the two isomers and the combined glucuronides represented 68% of the total.

APPEARS THIS WAY ON ORIGINAL

The following tables were copied from the submission (V 45/p88-91):